Draft Guidance for Industry and FDA Staff

Establishing the Performance Characteristics of *In Vitro* Diagnostic Devices for the Detection of *Helicobacter pylori*

DRAFT GUIDANCE

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You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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When final, this document will supersede Review Criteria for Assessment of Laboratory Tests for the Detection of Antibodies to *Helicobacter Pylori* dated September 17, 1992.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Division of Microbiology Devices

Preface

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Establishing the Performance Characteristics of *In Vitro* Diagnostic Devices for the Detection of *Helicobacter pylori*

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the number listed on the title page of this guidance.

I. Introduction

FDA is issuing this draft guidance to provide industry and agency staff with updated recommendations concerning 510(k) submissions for various types of *in vitro* diagnostic devices (IVDs) intended to be used for detecting *Helicobacter pylori (H. pylori).* The document is a revision of the guidance entitled "Guidance for Industry and FDA Staff: Review Criteria for Assessment of Laboratory Tests for the Detection of Antibodies to *Helicobacter pylori*" that was issued on September 17, 1992. It is updated to include alternate test methods, other than antibody-based detection, that are currently being used to detect *H. pylori*. Such methods, discussed in this document, include the stool antigen test, the urease test, blood and urine antibody tests, and the carbon-urea breath test.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

This document recommends studies for establishing the performance characteristics of diagnostic devices for the direct or indirect detection of *H. pylori* bacteria in human blood, serum, urine, stool or breath specimens. FDA believes that these recommended studies will be relevant for premarket notification [510(k)] submissions for these types of tests.

A manufacturer who intends to market an IVD device for detecting *H. pylori* bacteria in human specimens must conform to the general controls of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). In addition, unless exempt, they must obtain premarket clearance or approval prior to marketing the device (sections 510(k), 513, 515 of the FD&C Act; 21 U.S.C. 360(k), 360c, 360e).

This document is intended to supplement 21 CFR 807.87 (information required in a premarket notification) and other FDA resources such as "Premarket Notification: 510(k)"**,** http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.

III. Scope

This document recommends studies for establishing the performance characteristics of IVDs for the detection of *H. pylori* in human specimens. Detection methods listed in this guidance include blood and urine antibody tests, stool antigen test, carbon- 13 (^{13}C) urea breath and blood tests, and the urease test.

The scope of this document is limited to the devices described in existing classifications, as indicated below.

The following are the existing *H. pylori* IVD classification regulations:

> **21 CFR 866.3110 *Campylobacter fetus* serological reagents**
>
> (a) *Identification*. *Campylobacter fetus* serological reagents are devices that consist of antisera conjugated with a fluorescent dye used to identify *Campylobacter fetus* from clinical specimens or cultured isolates derived from clinical specimens. The identification aids in the diagnosis of diseases caused by this bacterium and provides epidemiological information on these diseases. *Campylobacter fetus* is a frequent cause of abortion in sheep and cattle and is sometimes responsible for endocarditis (inflammation of certain membranes of the heart) and enteritis (inflammation of the intestines) in humans.
>
> (b) *Classification*. Class I (general controls).

Devices within the classification described in 21 CFR 866.3110 are Class I devices that require premarket notification.

The following are the product codes for *H. pylori* devices cleared under 21 CFR 866.3110:

LYR – *H. pylori*
MSQ – Tests Urea (Breath or Blood)

Therefore the following information should be included in your submission:

- The diagnostic marker for the device (i.e., ^{13}C, antigens, or antibodies)
- Methodology or test principle of the device (e.g., Immunoassay, Chemiluminescence assay, etc.)
- Sample preparation methods
- Length of time taken to report results (e.g., within 6-24 hours of the beginning the test, etc.)

IV. Risks to Health

H. pylori is a gram-negative, microaerophilic bacterium that inhabits the stomach and duodenum. Infection by this organism may cause a chronic, low-level inflammation of the stomach lining, which is linked to the development of duodenal and gastric ulcers and stomach cancer. Over 80% of individuals infected with the bacterium are asymptomatic; however, some develop serious problems, such as stomach or duodenal ulcers. Common complaints include pain or discomfort (usually in the upper abdomen), bloating, feeling full after eating a small amount of food, lack of appetite, nausea, vomiting, and dark or tar-colored stools. Ulcers that bleed can cause a low blood count and fatigue. More than 50% of the world's population harbor *H. pylori* in their upper gastrointestinal tract. Infection is more prevalent in developing countries. The route of transmission is unknown, although individuals typically become infected in childhood [Ref. 1, 2].

H. pylori detection includes capillary blood, serum, and urine antibody tests (i.e., detection of IgG, IgA, and/or IgM monoclonal antibodies against various *H. pylori* epitopes, stool antigen tests, and ^{13}C-urea breath/blood test,in which the patient ingests ^{13}C-labeled urea. The bacteria metabolize this urea producing labeled carbon dioxide that can be detected in the breath), and/or microbial culture. The performance of these devices can be affected by some drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, and antibiotics, which can affect *H. pylori* urease activity and may give false negative results with the urea-based tests. Atrophy of the gastric mucosa, due to chronic *H. pylori* infection, can also cause false negative results [Ref. 3, 4].

Failure of devices for detection of *H. pylori* to perform as expected or failure to interpret results correctly may lead to incorrect patient management decisions. In the context of individual patient management, a false negative report could lead to delays in providing (or failure to provide) definitive diagnosis, appropriate treatment, infection control and prevention measures. A false

positive report could lead to unnecessary or inappropriate treatment or unnecessary control and prevention actions. Therefore, establishing the performance of these devices and understanding the risks that might be associated with the use of these devices is critical to their safe and effective use.

The studies conducted by manufacturers to establish the performance of *H. pylori* detection devices are the basis for determining the safety and effectiveness or substantial equivalence of these devices. Confirmatory tests recommended by the Division of Microbiology Devices, with regard to the use of endoscopic diagnostic tests to diagnose *H. pylori* infection, are outlined in Appendix A.

V. Establishing Performance Characteristics

We recommend that you provide a copy of your study protocols. These protocols should include information regarding exclusion and inclusion criteria, comparative methods used in the study, type and number of specimens used, directions for use, and a scientifically sound statistical analysis plan. These protocols will enable us to better interpret your data and thus expedite review of your submission.

When referring to Clinical Laboratory Standards Institute (CLSI) standards or guidelines, we recommend that you indicate which specific aspects of the standards or guidelines you followed. In addition, you should specify whether you modified any part(s) of the standard and describe these modifications.

We encourage sponsors to contact the Division of Microbiology Devices to request a review of their proposed studies and selection of specimen types. We particularly encourage manufacturers to seek this type of discussion if they have difficulty obtaining samples.

A. General Recommendations

The Division of Microbiology Devices recommends the use of endoscopic diagnostic tests to confirm and exclude the diagnosis of *H. pylori* infection. The number of positive or negative tests required depends on whether these tests are to be used for the initial diagnosis (before treatment, to confirm infection) or used to document eradication (after the completion of therapy). The definitions of baseline infection and eradication following therapy need to be considered separately (in terms of the number and type of endoscopic tests used) since at baseline it is important to achieve high specificity (low false positives) to confirm infection while at the test-of-cure time point sensitivity is more important to exclude infection (low false negatives). Definitions of infection (or no infection) have been developed to assist sponsors in deciding which patients should be considered infected, not infected, or not evaluable based on endoscopic tests. It is important to note that there is no single correct definition of these terms. True definitions are based on the quality and quantity of endoscopic *H. pylori* diagnostic tests.

The Division maintains that inclusion into a clinical study only requires a single positive urease test, but evaluability for analysis requires either a positive culture or both a positive urease test and positive histology. If the culture is negative or missing and the histology/urease test results are incongruent, these patients should be considered non-evaluable. (See Appendix A for additional information).

B. Controls

When conducting the performance studies described below, we recommend that you run appropriate external controls every day of testing for the duration of the analytical and clinical studies. Examples of appropriate external controls include clinical specimens previously characterized as being positive or negative for H. pylori, or commercially available positive and negative controls.

C. Analytical Studies

We recommend you perform the following studies:

Antigen Characterization

You should describe the antigen used in the device as a substrate. Briefly describe the production of antigen, strain of organism, purification process, etc. (You may label this as "Proprietary Information"). If the antigen you employ is a native antigen, you should identify its source. In addition, we recommend you provide a rationale for the selection of the antigen.

Validation of Reactive Cut-off

We recommend that you describe and explain the rationale for how you determined the reactive cut-off value for your device. If you included clinical data, you should identify the number of patients enrolled and treated in the study, the patient population, and methods used to determine the presence of *H. pylori* for diagnosis in these patients. The data should be presented graphically.

Analytical Sensitivity

Limit of Detection
We recommend that you determine the limit of detection (LoD) using serial dilutions (in triplicate) of the *H. pylori* analyte to calculate the analytical sensitivity for serological assays and stool antigen tests. The LoD is defined as "the concentration of *H. pylori* antigen/antibody in a specimen that gives a 95% detection rate." The LoD may be confirmed by preparing at least 20 additional replicates at the LoD concentration and demonstrating that the antigen, antibody, or bacteria were detected 95% of the time.

In addition, we recommend that you describe the sample type, define your measures of sensitivity, provide your acceptance criteria, or provide a data summary that clarifies how measurements below the level of sensitivity are reported to the user. We suggest that you refer to CLSI document EP17-A [Ref. 5] when designing your studies.

Analytical Specificity

Cross Reactivity
We recommend that you test for potential cross-reactivity with similar organisms (see Table 1 below). For breath tests, you should include organisms such as Proteus species, which inhabit the stomach and may produce urease. We recommend that you identify the bacteria and confirm their titers. Bacteria should be evaluated at 10^7 cfu/ml or higher. We encourage sponsors to present the results from the cross-reactivity studies for devices detecting multiple pathogens in a tabular format to include organism type and concentration of organisms tested in cfu/mL.

We encourage sponsors to present the results from the cross-reactivity studies for devices detecting multiple pathogens using the display format shown in Table 1.

Table 1. Microorganisms recommended for analytical specificity (cross-reactivity) studies.

Organism	***In vitro* diagnostic test type**			
	Serum/Whole Blood Antibody	Stool Antigen	Urine Antibody	Urease Breath
Campylobacter spp.	√	√	√	
Bacillus spp.	√	√	√	
Clostridium spp.	√	√	√	
Enterobacter spp.	√	√	√	
Clostridium spp.	√	√	√	
Candida albicans	√	√	√	
Pseudomonas spp.	√	√	√	
Borrelia burgdorferi	√	√	√	
E. coli	√	√	√	
H. influenzae	√	√	√	
Proteus spp.				√

Interference
We recommend that you conduct a comprehensive interference study using medically relevant concentrations of the interferent to assess the potentially inhibitory effects of substances encountered in specimens. You should test interference at the assay cut-off determined for your assay. Please refer to the CLSI Document EP7-A, "Interference Testing in Clinical Chemistry; Approved Guideline" (2002) [Ref. 6] for additional information on experimental designs, including guidelines for selecting interferents.

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Potentially interfering substances include, but are not limited to, the following: leukocytes, intestinal secretions or mucus, fat, and medications used to relieve diarrhea or other gastric symptoms. In addition, some drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), can affect *H. pylori* urease activity and give false negative results with the urea-based tests.
We recommend that you include the following items:

- types and levels of interferents tested
- concentrations of *H. pylori* antigen in the sample
- number of replicates tested (at least 3)
- definition or method of computing interference

In addition, you should identify any observed trends in bias (i.e., negative or positive) and indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone. We recommend that you state the criteria or level for determining non-interference.

You may not need to perform additional interference testing with potential interferents of your assay that have already been identified in literature or by other sources. However, we recommend that you include them in the labeling.

Precision

Within Laboratory Precision/Repeatability
We recommend that you conduct within-laboratory precision studies for devices that include instruments or automated components. You may perform these studies in-house, i.e., within your own company. In addition, you should test sources of variability (such as operators, days, assay runs, etc.) for a minimum of 12 days (not necessarily consecutive), with two runs per day, and two replicates of each sample per run. These test days should span at least two calibration cycles. The test panel should consist of three *H. pylori* samples that include:

- A "high negative" sample (C_5 concentration): a sample with an analyte concentration below the clinical cut-off such that results of repeated tests of this sample are negative approximately 95% of the time (and results are positive approximately 5% of the time).

- A "low positive" sample (C_{95} concentration): a sample with an analyte concentration just above the clinical cut-off such that results of repeated tests of this sample are positive approximately 95% of the time.

- A "moderate positive" sample: a sample with an analyte concentration at which one can anticipate positive results approximately 100% of the time (e.g., approximately two to three times the concentration of the clinical cut-off).

For information and guidelines for experimental design, computations, and a format for stating performance claims for these studies, you may refer to the CLSI Document EP5-A2, "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline" (1999) [Ref. 7].

For this internal investigation, you may use pooled patient samples and quality control materials supplied, or recommended for use, with your device.

You should include the items listed below:

- point estimates of the concentration
- standard deviations of within-run and total precision
- sites at which precision protocol was run
- number of days, runs, and observations
- number of sites and/or operators

We recommend that you identify which factors (e.g., reagent lots, operators) remained constant, which were varied during the evaluation, and describe the computational methods you employed if they are different from that described in CLSI EP5-A2. "Evaluation of Precision Performance of Clinical Chemistry Devices, Approved Guideline (1999) [Ref. 7].

CLSI documents EP5-A2 [Ref. 7] and EP12-A [Ref. 8] contain further information about designing and performing precision studies.

Reproducibility

The protocol for the reproducibility study may vary slightly depending on the assay format. As a general guide, we recommend the following protocol:

- Evaluate the reproducibility of your test at three testing sites (i.e., two external sites and one in-house site).
- Use a 5-day testing protocol that includes a minimum of two runs per day, (unless the assay design precludes multiple runs per day) and three replicates of each panel member per run.
- Have at least two operators at each facility perform the test every day. We recommend that for rapid testing or point-of-care devices, you include a larger number of devices in your evaluation in order to mimic the settings in which the devices will be used.
- Use the same sample panel as described in the repeatability study above.

The CLSI document, EP15-A2 [Ref. 9], contains additional information on reproducibility study design.

<u>Specimen Storage and Shipping Conditions</u>

If you recommend specimen storage conditions, you should demonstrate that your device generates equivalent results for the stored specimens at several time points throughout the duration of the recommended storage and at both ends of your recommended temperature range. If special selective/transport medium (e.g., BHI-VAN broth) is recommended for storage or shipping, you should conduct appropriate studies to demonstrate that the device will perform as described when the specimen is preserved in such media.

D. Clinical Performance Studies

We recommend that you conduct prospective clinical studies to determine the performance of your device for all the specimen types you claim in your labeling. We recommend that you compare your device to an established method or "gold standard" dependent on the analyte being detected for *H. pylori* assays. Endoscopic biopsy followed by histopathologic confirmation, culturing of the organism, and a urease detection assay is considered the gold standard. The presence of *H. pylori* can be demonstrated in histological specimens by various stains including, but not limited to, Geimsa, the Warthin-Starry silver stain, acridine orange, and hematoxylin and eosin [Ref. 3]. Culturing *H. pylori* from patient specimens requires microaerophilic conditions and the use of specialized media. The incubation period before growth is visibly seen is from 3 to 4 days and can be up to 7 days. The culture isolates are identified as *H. pylori* by the use of morphology, oxidase, and catalase reactions and a positive rapid urease test. *H. pylori* is a rapid and prolific producer of a urease enzyme. This unique phenotypic characteristic of this bacterial species is the basis for a presumptive test for its presence. A portion of the biopsy sample is evaluated for urease by inoculation into urea broth or agar. A positive test is indicated by a change in the color of the medium based on alkalinity. This is a presumptive test for the presence of the organism when it stands alone and confirmation is by culturing the microbe.

Study Protocol

We strongly suggest that you develop a detailed study protocol that includes, for example,

1. Patient inclusion and exclusion criteria,
2. The type and number of specimens needed,
3. Complete directions for use, and
4. a statistical analysis plan that accounts for variances to prevent data bias.

You should include this and any other relevant protocol information in your premarket submission, such as:

1. The patient population to be tested: Risk factors include previous use of antimicrobials, exposure to H. pylori, exposure to gastric acid suppressants, poor host serum immunoglobulin levels, advanced age, and severity of underlying illness of the host.

2. Disease caused by *H. pylori* that may be diagnosed.

3. Specimen types for which testing will be indicated. Liquid or unformed stool is the preferred specimen type. Formed stool is not acceptable.

4. Settings in which specimens are to be collected and the type of facility where testing with the device will be conducted.

We encourage sponsors to contact the Division of Microbiology Devices to request a review of their proposed studies and selection of specimen types.

Specimen Type(s)

We recommend that you include a sufficient number of prospectively collected samples for each specimen type (e.g., blood, stool, etc.,) such that your data generates a sensitivity result with a lower bound of the two-sided 95% confidence interval (CI) that is greater than 90%. Generally, we recommend testing a statistically significant number of samples determined to be positive using the reference method for each specimen type. You may use either fresh or archived frozen samples. If both fresh and frozen samples are tested, you should analyze the data separately. If a limited number of samples are available, we recommend that you contact the Division of Microbiology Devices to discuss alternative proposals.

Study Sites

We recommend that you conduct your studies at a minimum of three clinical sites. Clinical investigations of unapproved and uncleared *in vitro* diagnostic devices, including diagnostic devices for *H. pylori* are subject to the investigational device exemption (IDE) provisions of Section 520(g) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360j). You should consider how 21 CFR part 812 applies to your particular study and refer to 21 CFR part 50 (informed consent), and 21 CFR part 56 (institutional review board review) for other applicable requirements. Investigational devices that detect novel bacterial strains may meet the definition of "significant risk device" in 21 CFR 812.3(m). Clinical investigations of significant risk devices require the submission of an IDE application to FDA for review and approval, in accordance with 21 CFR part 812 (21 CFR 812.20).

We recommend that the performance evaluation for devices intended for point-of-care use or rapid testing include, at a minimum, one site at a clinical laboratory as well as sites representative of non-laboratory settings in which the device is intended to be used (e.g., physician's office, emergency department). In order to determine whether training of the person conducting the test is likely to affect the performance of the device, you should conduct testing both at a clinical laboratory with more experienced and trained personnel, as well as at non-laboratory sites in which the device is intended to be used even though operators will likely have less laboratory training. In addition, you should provide the names of the investigators and the sites where samples were obtained. You should also describe or provide the clinical study protocol used at each site.

Study Population

As the diagnosis of *H. pylori* infection is based on both clinical signs and symptoms in addition to the presence of *H. pylori*, the serum samples should be obtained from patients

who are symptomatic for gastritis. Each patient should have a clinical diagnosis which may be used when trying to explain discrepant test results. These results should not be used to change the initial results of the test. You should describe how the presence of *H. pylori* was determined in these patients.

You should present the data showing how the test-results compare to the established reference methods. We recommend that you develop a robust Statistical Analysis Plan for presenting comparative test results. (You should refer to "*Guidance for Industry and FDA Staff: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests, March 13, 2007*" at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm).

These results should be displayed in tabular format with positive, negative, and equivocal results shown, (i.e., a 2 x 2 table showing agreement between the new assay (rows) versus the reference method or gold standard (columns)). You may include an explanation for resolution of discrepant results and identify all repeated test results; however, these results should not be used to change the initial results of the test.

In addition, the clinical diagnosis of the patient may also be used to explain test results. The device's diagnostic sensitivity and specificity should be presented in the Performance Characteristic section of the Product Insert based on comparison to biopsy (culture and/or histological diagnosis) or the urea breath test. Additional correlation data may be presented to another legally marketed device or the detection of *H. pylori* antibodies.

E. CLIA Waiver

If you are seeking waiver for your device under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), we recommend that you consult with the Division of Microbiology Devices staff regarding the design of specific studies to support the CLIA waiver application for your device. The guidance for industry and FDA staff, "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications," is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm079632.htm.

VI. References

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4. Graham DY, Shiotani A (June 2008). "New concepts of resistance in the treatment of *H. pylori* infections". Nat Clin Pract Gastroenterol Hepatol 5 (6): 321–31

5. Clinical and Laboratory Standards Institute. 2004. Protocol for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (EP17-A)

6. Clinical and Laboratory Standards Institute. 2005. Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (EP07-A2)

7. Clinical and Laboratory Standards Institute. 2004. Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition (EP05-A2)

8. Clinical and Laboratory Standards Institute. 2008. User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline— Second Edition (EP12-A2)

9. Clinical and Laboratory Standards Institute. 2005. User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (EP15-A2)

10. Clinical and Laboratory Standards Institute. 2004. Quality Control for Commercially Prepared Microbiological Culture Media; Approved Standard—Third Edition (M22-A3)

11. CDC NIH manual, Biosafety in Microbiological and Biomedical Laboratories, 3rd Edition, 1993

12. Clinical and Laboratory Standards Institute., Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue Approved Guideline (M29-A)

Appendix A -. Use of endoscopic diagnostic tests to diagnose *H. pylori* infection

Pre-therapy Diagnosis				Post-therapy Diagnosis			
Test Result			Patient Status	Test Result			Patient Status
Cult	Hist	Urease		Cult	Hist	Urease	
Three Tests Available							
+	+/-	+/-	Infected	+	+/-	+/-	Infected
-	+	+	Infected	-	+	+	Infected
-	-	+	Not infected	-	-	+	Infected
-	+	-	Not infected	-	+	-	Infected
-	-	-	Not infected	-	-	-	Eradicated
Two Tests Available							
+	+	N/A	Infected	+	+	N/A	Infected
+	-	N/A	Infected	+	-	N/A	Infected
-	+	N/A	Not evaluable	-	+	N/A	Infected
-	-	N/A	Not infected	-	-	N/A	Eradicated
+	N/A	+	Infected	+	N/A	+	Infected
+	N/A	-	Infected	+	N/A	-	Infected
-	N/A	+	Not evaluable*	-	N/A	+	Infected
-	N/A	-	Not infected	-	N/A	-	Eradicated
N/A	+	+	Infected	N/A	+	+	Infected
N/A	+	-	Not evaluable	N/A	+	-	Infected
N/A	-	+	Not evaluable*	N/A	-	+	Infected
N/A	-	-	Not infected	N/A	-	-	Eradicated
One Test Available							
+	N/A	N/A	Infected	+	N/A	N/A	Infected
-	N/A	N/A	Not evaluable	-	N/A	N/A	Not evaluable
N/A	N/A	+	Not evaluable*	N/A	N/A	+	Infected
N/A	N/A	-	Not evaluable	N/A	N/A	-	Not evaluable
N/A	+	N/A	Not evaluable	N/A	+	N/A	Infected
N/A	-	N/A	Not evaluable	N/A	-	N/A	Not evaluable

N/A Indicates not evaluable or missing result

* Patients with a single positive urease test at baseline may be more appropriately considered infected.